A Versatile Palladium-Mediated Three-Component Reaction for the One-Pot Synthesis of Stereodefined 3-Arylidene-(or 3-Alkenylidene-)tetrahydrofurans

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A one-pot reaction between equimolecular amounts of various propargyl alcohols, Michael acceptors, and unsaturated halides (or triflates) in the presence of a palladium(0) catalyst provides a simple and flexible entry into highly substituted 3-arylidene-(or 3-alkenylidene-)tetrahydrofurans. The efficiency of this palladium-mediated three-component reaction has been shown to be strongly influenced by the nature of the catalyst system, and in this regard, a palladium(0) catalyst generated in situ by reduction of $PdCl_2(PPh_3)_2$ with *n*-butyllithium has been found particularly effective.

Introduction

Five-membered oxygen heterocycles are important synthetic targets due to their occurrence in numerous natural products,[1] their wide range of biological activities,[2] and their utility as versatile intermediates.[3] This important class of heterocyclic products has therefore stimulated the development of new synthetic methodologies.[4] During the past few years, in addition to radical chemistry, transition metal-mediated synthesis has emerged as one of the most powerful tools for the construction of these subunits.[5] Over the same period, multicomponent condensations have gained considerable interest in the field of heterocycle synthesis due to their potential of generating molecular diversity in a single synthetic step from simple, readily available, starting materials.[6] In this area, methodologies based on palladium-catalyzed cascade reactions are of particular importance owing to the diversity of bond-forming processes available, the mildness of reaction conditions, the high levels of chemo-, regio-, and stereoselectivities, and the excellent functional group tolerance.[7]

As part of our ongoing program in heterocyclic synthesis, we recently undertook the development of multicomponent condensation reactions based on palladium-mediated cyclization processes devised in our laboratory and aimed at the preparation of highly functionalized tetrahydrofurans.[8] The underlying goal of this study was to devise a methodology that would ultimately be utilizable in a combinatorial way. With this aim, we recently succeeded in developing a one-pot three-component condensation that combines three readily available and inexpensive materials: an allylic alcohol, an activated olefin, and an unsaturated halide to yield 4-benzyltetrahydrofuran-3,3-dicarboxylates (Scheme 1). The methodology consisted in an oxygen nucleophile initiated Michael addition followed by a carbopalladation reaction.[9] Unfortunately, this approach suffered from several drawbacks that impaired its combinatorial potential. Of

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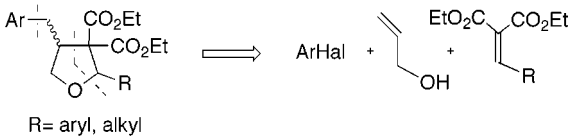
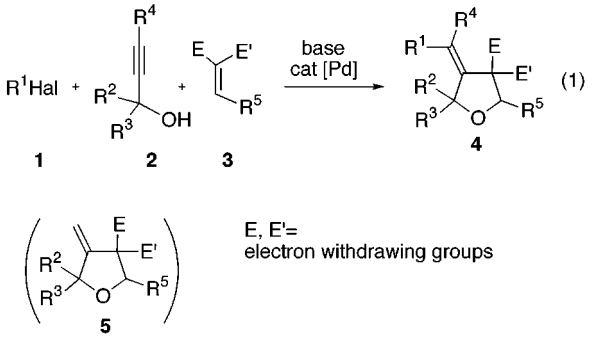
Scheme 1. Retrosynthetic Analysis of Ethyl 4-Benzyltetrahydrofuran-3,3-dicarboxylates



particular importance was the reluctance of secondary and tertiary alcohols to participate in the reaction, thus restricting the choice to the simple allyl alcohol. Another important limitation was the necessity of using impractical slow addition techniques in order to avoid undesirable competitive reactions. Excess reagents were also needed to bring the reactions to completion, rendering the isolation of the products tedious and time-consuming.[10]

Ideally, a practical procedure would consist of simply mixing equal amounts of each of the three partners and treating them with a catalytic quantity of a palladium complex at room temperature. To this end, it was decided to substitute allylic alcohols for their propargylic analogues because of their high reactivity generally observed in similar carbocyclization reactions.[9] This would produce a new class of valuable stereodefined arylidenetetrahydrofurans (eq 1). Another advantage of this alternative would be that a greater diversity in structure may be produced if disubstituted acetylenic substrates were involved in the process. The results of this study are reported below.



Results and Discussion

The first assays to determine the viability of propargylic nucleophiles participating in the cascade Michael addition−carbocyclization process were carried out by using conditions slightly different from those previously used in reactions involving allylic alcohols. As mentioned above, one important feature of the new procedure is that stoichiometric amounts of each of the three partners are reacted simultaneously. THF as solvent was also preferred to DMSO for practical reasons. Thus, treatment of propargyl alcohol **(2a)** with 1 equiv of *n*-BuLi in THF was followed by addition of diethyl benzylidenemalonate **(3a)** and phenyl iodide **(1a)**. Upon heating the reaction mixture (up to 50 °C) in the presence of 5 mol % of a Pd^0/(dppe) catalyst,[11] we observed the formation of two cyclic products identified as the desired arylidenetetrahydrofuran **4a** and the 3-methylenetetrahydrofuran **5a** (2:1 mixtures as shown by NMR analysis). The undesired byproduct undoubtedly arose from another palladium-mediated reaction recently reported by us, which involves a palladium hydride species as an electrophilic partner rather than the phenylpalladium iodide needed in the three-component condensation reaction.[9a] Minimizing this competitive two-component cyclization process proved less problematic than expected. In a first set of experiments, a range of phosphine ligands such as triphenylphosphine, tris-furylphosphine, tris-(*p*-fluoro)phenylphosphine, dppb, and dppf were screened.[11] It emerged that the nature of the catalytic system had a negligible effect on the final product distribution. Nevertheless, these experiments showed that the PPh_3 ligand was much more effective in terms of yields and reaction times. Turning our attention to possible solvent effects, it was found that the use of DMSO completely inhibited the formation of the side product.[12] Thus, effecting the reaction in a 1/1 mixture of THF/DMSO in the presence of 5 mol % of a Pd^0/(PPh_3) catalyst produced **4a** within 1 h as the sole product in 55% yield. Another significant improvement came later from the utilization of a palladium complex generated by reduction of $PdCl_2(PPh_3)_2$ with *n*-BuLi. By using 5 mol % of this catalyst, the reaction took place at *room temperature in less than 15 min*, leading to the exclusive formation of **4a** in up to 89% isolated yield. The amount of catalyst could be considerably decreased (1 mol %) without significant loss in the yield (70% yield), albeit a prolonged reaction time was needed (3 h).

With this model study in hand, we sought to investigate various combinations of unsaturated halides, propargylic alcohols, and activated olefins. The generality of the methodology was firmly demonstrated by the variety of tetrahydrofurans that could be produced. The results are summarized in Table 1. Almost all aryl iodides gave satisfactory results (entries 1−6, 9−21), particularly those having electron-donating substituents. The presence of an ester in the aromatic ring was tolerated in the reaction (entry 3). Some limitations were nevertheless encountered with other unsaturated compounds. Indeed, phenyl bromide, 2-bromopropene, and phenyl triflate led to the formation of complex mixtures of unidentified products. However, *β*-bromostyrene (**1g**) and cyclohexenyl triflate (**1h**) took part in the coupling process in satisfactory yields (entries 7 and 8). As vinylic triflates can be easily prepared from the corresponding ketones, their use in the present reaction would greatly expand the range of accessible products. Varying the activated olefin component, it was observed that a variety of arylidenemalonates, having electron-withdrawing or electron-donating substituents, participated well in the three-component reaction (entries 9−15, and 21). The reaction also proceeded with Michael acceptors bearing alkyl chains (entry 16). In marked contrast with what was observed with allylic alcohols, the present reaction showed wide structural flexibility with respect to the propargylic alcohol component. Although requiring more elevated temperatures in some cases in order to proceed

(10) In a typical procedure, the alkoxide was generated by treatment of allyl alcohol (2 equiv) with *n*-BuLi at 0 °C and added via a syringe pump to a heated (50 °C) solution of the Michael acceptor (1 equiv), the aryl iodide (1.5 equiv), and the catalyst. The reaction did only proceed in DMSO.

(11) The Pd^0 catalysts were preformed by reaction of palladium acetate with 2 equiv of monodentate phosphine (alternatively 1 equiv of bidentate phosphine) per palladium followed by addition of 1-hexene as reducing agent. Dppe = 1,2-bis(diphenylphosphino)ethane; dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1, 1′-bis(diphenylphosphino)-ferrocene.

(12) Accordingly, the two-component condensation was attempted in DMSO under the conditions previously described for this reaction (see ref 9a), but failed to produce the expected 3-methylenetetrahydrofuran.

Table 1. Synthesis of Tetrahydrofurans from Unsaturated Halides (or triflates), Propargyl Alcohols, and Benzylidene (or alkylidene) Malonates[a]

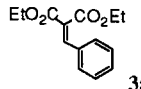
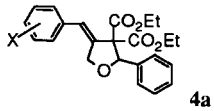
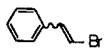
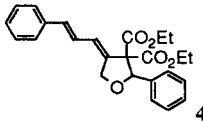
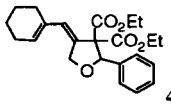
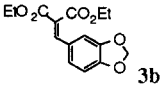
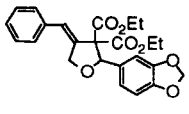
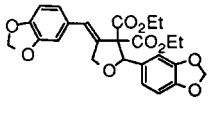
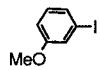
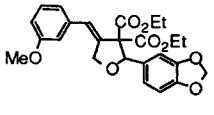
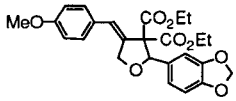
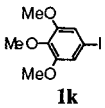
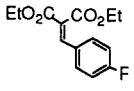
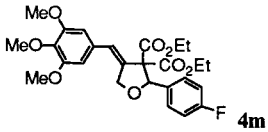
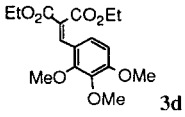
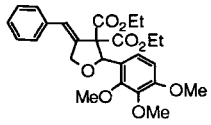
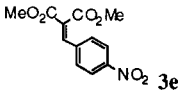
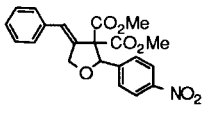
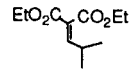
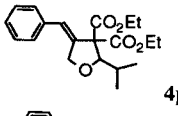
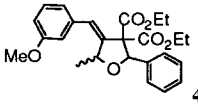
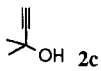
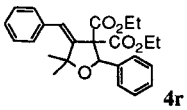
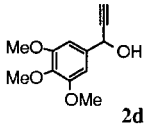
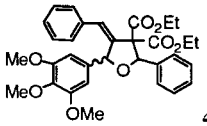
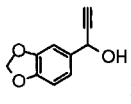
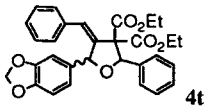
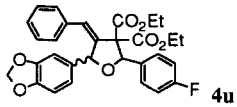
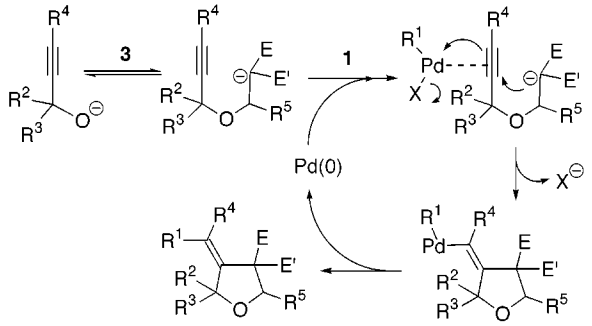
Entry	Halide (or triflate)	Propargylic alcohol	Activated olefin	cat. mol%	T (°C)	time (h)	Product	Yield (%)[b]
1	 X= H **1a**	 **2a**	 **3a**	5 2.5 1	25 25 25	0.25 0.5 3	 **4a**	89 78 70
2	*m*-CF_3 **1b**			5	25	2	**4b**	50
3	*p*-CO_2Me **1c**			5	25	3	**4c**	46
4	*p*-Me **1d**			5	25	0.75	**4d**	55
5	*p*-OMe **1e**			5	25	1	**4e**	80
6	*o*-OMe **1f**			5	25	3	**4f**	50
7	 **1g**	**2a**	**3a**	5	25	1.5	 **4g**	55
8	 **1h**	**2a**	**3a**	5	25	1	 **4h**	80
9	**1a**	**2a**	 **3b**	2.5	25	1	 **4i**	69
10	 **1i**	**2a**	**3b**	5	25	1.5	 **4j**	90
11	 **1j**	**2a**	**3b**	5	25	1.5	 **4k**	66
12	**1e**	**2a**	**3b**	2.5	25	1	 **4l**	78
13	 **1k**	**2a**	 **3c**	5	25	2	 **4m**	56
14	**1a**	**2a**	 **3d**	2.5	25	3	 **4n**	51
15	**1a**	**2a**	 **3e**	5	25	0.5	 **4o**	66
16	**1a**	**2a**	 **3f**	5	25	1.5	 **4p**	64
17	**1a**	 **2b**	**3a**	5	30	2	 **4q**	71[c] (1.5:1)
18	**1a**	 **2c**	**3a**	5	50	0.75	 **4r**	53[d]
19	**1a**	 **2d**	**3a**	5	55	6	 **4s**	50[c] (1:1)

Table 1. (Continued)

Entry	Halide (or triflate)	Propargylic alcohol	Activated olefin	cat. mol%	T (°C)	time (h)	Product	Yield (%)[b]
20	**1a**	 **2e**	**3a**	5	25	5	 **4t**	60[c] (1:1)
21	**1a**	**2e**	**3c**	5	55	5	 **4u**	60[c] (1:1)

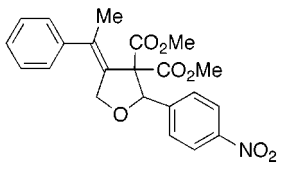
[a] All reactions were performed on a 1 mmol scale using equimolar amounts of each component. [b] Yields refer to pure isolated products. [c] Mixture of diastereomers. Ratios are indicated in brackets. [d] Not isolated as a pure product (see text). Yield determined by ^{1}H NMR analysis.

Scheme 2

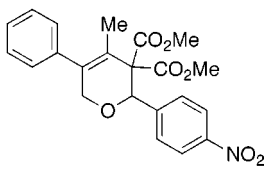


efficiently, secondary alcohols furnished the corresponding tetrahydrofurans in reasonable yields. In those cases, essentially 1:1 mixtures of the cis and trans diastereomers were obtained (entries 17, 19−21). 2-Methyl-3-butyn-2-ol (**2c**) also underwent cyclization but yielded an inseparable 2.5:1 mixture of the expected tetrahydrofuran and the corresponding and previously reported[9a] 3-methylenetetrahydrofuran (entry 18).

To further explore the scope and generality of the reaction, we next examined the behavior of disubstituted acetylenic alcohols. As an example, reaction of **1a** with 2-butyn-1-ol and dimethyl (4-nitro)benzylidenemalonate proceeded smoothly at 40 °C leading after 7 h to the formation of two inseparable isomeric heterocycles. These were identified as the tetrahydrofuran **6** and the dihydropyran **7** (4:1 ratio; 57% combined yield) by using ^{1}H, ^{13}C, HMBC, and NOESY NMR experiments.



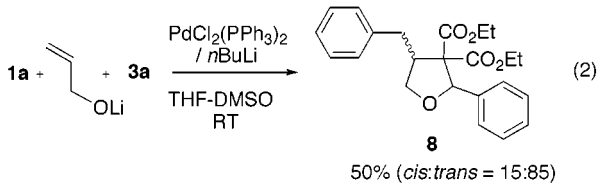
6



7

The structure of compound **6** again suggests a concerted 5-*exo* cyclization process that consists of an intramolecular nucleophilic attack of the enolate intermediate onto the tethered unsaturation activated by the organopalladium species (Scheme 2).[8] The dihydropyran **7** would therefore result from a competitive 6-*endo* cyclization process.

Stimulated by these interesting results, we briefly revisited the reaction of allylic alcohols using our new protocol. We were pleased to find that *allyl alcohol reacted at room temperature with equimolar amounts* of **1a** and **3a** to yield the expected tetrahydrofuran **8** in 50% isolated yield (eq 2). However, the reaction proceeded slowly (24 h), and nonnegligible amounts of side-products were also formed. Since purification problems still remained, this study was not pursued.



50% (*cis*:*trans* = 15:85)

Conclusion

The present three-component reaction makes an interesting and valuable complement to our recently described tetrahydrofuran synthesis involving allyl alcohol. The methodology is extremely practical and versatile in that a range of readily available propargylic alcohols, unsaturated halides or triflates, and activated olefins can be reacted without using slow addition techniques. Essentially no side reaction was observed under the optimized procedure, rendering the isolation of the products very easy. With such features, the protocol described in this paper holds promise for the preparation of tetrahydrofuran libraries. Future work will focus on the reactivity of olefins bearing electron-withdrawing groups other than esters as an additional element of diversity. Extension of our methodology to the preparation of other heteroatom-containing cyclic compounds is already underway.

Experimental Section

General Methods. All reactions were carried out under a nitrogen atmosphere using standard syringe, cannula, and septa techniques. Commercial reagents were used as purchased: Aryl halides were commercially available except for 5-iodo-1,2,3-trimethoxybenzene[13a] and 4-iodo-1,2-(methylenedioxy)-benzene.[13b] Noncommercial propargylic alcohols were synthesized by standard propargyl anion chemistry,[14] and Michael acceptors were prepared from the corresponding aldehydes applying conventional Knoevenagel condensations (catalytic

(13) (a) Bowden, B. F.; Read, R. W.; Taylor, W. C. *Aust. J. Chem.* **1981**, *34*, 799. (b) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662.

(14) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440.

piperidine, catalytic HOAc, toluene, reflux).[15] Tetrahydrofuran and dimethyl sulfoxide were distilled over calcium hydride. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminum-backed plates. Flash chromatography was performed using Merck silica gel 60 (40−63 μm). Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ) are quoted in parts per million. J values are given in hertz.

General Procedure for the One-Pot Three-Component Reaction. A stirred suspension of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) in DMSO (3 mL) was treated with *n*-BuLi (2.0 M in hexanes, 50 μL, 0.1 mmol) at room temperature, affording a dark-red homogeneous solution. In a separate flask, *n*-BuLi (2.0 M in hexanes, 500 μL, 1 mmol) was added dropwise to an ice-cooled solution of the propargylic alcohol (1 mmol) in THF (3 mL), and the solution was allowed to reach room temperature (15 min). The Michael acceptor (1 mmol), the unsaturated halide (1 mmol), and the palladium catalyst solution were then successively added to the reaction mixture. The advancement of the reaction was monitored by GC (following the disappearance of the Michael acceptor). The reaction was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: ethyl acetate/petroleum ether). Melting points, NMR, and analytical data of selected exemples are as follows (see the Supporting Information for all other examples).

Ethyl 4-benzylidene-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4a): solid; mp 95−97 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22−7.32 (M, 10H), 6.88 (s, 1H), 5.79 (s, 1H), 5.11 (dd, J = 13.6 and 2.2, 1H), 4.81 (dd, J = 13.6 and 2.6, 1H), 4.35 (q, J = 7.0, 2H), 3.84 (m, 1H), 3.54 (m, 1H), 1.35 (t, J = 7.0, 3H), 0.81 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.3, 167.9, 138.0, 137.3, 136.5, 128.6, 128.3, 128.0, 127.7, 126.9, 126.1, 84.8, 70.4, 69.7, 62.0, 61.4, 14.1, 13.5. Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found C, 72.52; H, 6.32.

Ethyl 4-cinnamylidene-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4g): solid; mp 92−94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27−7.50 (M, 10H), 6.73−6.58 (m, 3H), 5.77 (s, 1H), 5.12 (d, J = 13.7, 1H), 4.74 (d, J = 13.7, 1H), 4.37 (m, 2H), 3.83 (m, 1H), 3.53 (m, 1H), 1.34 (t, J = 7.2, 3H), 0.81 (t, J = 7.2, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.4, 168.2, 138.4, 138.0, 137.6, 137.2, 135.3, 129.1, 128.7, 128.4, 128.3, 127.2, 127.0, 125.1, 124.7, 85.8, 70.1, 69.2, 62.4, 61.8, 14.5, 13.8. Anal. Calcd for $C_{25}H_{24}O_5$: C, 73.87; H, 6.45. Found C, 73.29; H, 6.57.

Ethyl 4-(cyclohex-1-enylidene)-2-phenyl-tetrahydrofuran-3,3-dicarboxylate (4h): solid; mp 84−86 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44−7.26 (M, 5H), 6.25 (s, 1H), 5.70 (br s, 1H), 5.67 (s, 1H), 5.03 (d, J = 13.4, 1H), 4.66 (d, J = 13.4, 1H), 4.30 (q, J = 7.0, 2H), 3.78 (m, 1H), 3.46 (m, 1H), 2.14 (m, 4H), 1.60 (m, 4H), 1.30 (t, J = 7.0, 3H), 0.75 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.6, 168.2, 137.5, 135.1, 134.0, 130.8, 128.9, 128.1, 127.9, 126.8, 84.6, 70.2, 69.5, 61.8, 61.2, 27.9, 25.9, 22.8, 21.8, 14.1, 13.4. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found C, 71.85; H, 7.43.

Ethyl 4-(3-methoxy)benzylidene-2-(3,4-dioxymethylene)phenyl-tetrahydrofuran-3,3-dicarboxylate (4k): solid; mp 88−90 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−6.75 (M, 8H), 5.93 (s, 2H), 5.68 (s, 1H), 5.07 (dd, J = 13.7 and 2.2, 1H), 4.77 (dd, J = 13.7 and 2.7, 1H), 4.35 (q, J = 7.1, 2H), 3.91 (dq, J = 10.7 and 7.1, 1H), 3.83 (s, 3H), 3.71 (dq, J = 10.7 and 7.1, 1H), 1.30 (t, J = 7.0, 3H), 0.75 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.3, 167.9, 159.7, 147.5, 147.3, 138.3, 137.8, 130.1, 129.6, 126.0, 121.1, 120.5, 114.3, 113.2, 107.9, 107.6, 100.1, 84.6, 70.3, 69.5, 62.1, 61.5, 55.3, 14.1, 13.7. Anal. Calcd for $C_{25}H_{26}O_8$: C, 66.07; H, 5.77. Found C, 65.82; H, 6.00.

Methyl 4-benzylidene-2-(4-nitro)phenyl-tetrahydrofuran-3,3-dicarboxylate (4o): solid; mp 141−143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, J = 8.8, 2H), 7.68 (d, J = 8.8, 2H), 7.46−7.29 (M, 5H), 6.85 (s, 1H), 5.84 (s, 1H), 5.13 (dd, J = 13.6 and 2.2, 1H), 4.84 (dd, J = 13.6 and 2.7, 1H), 3.92 (s, 3H), 3.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 167.9, 147.9, 144.4, 136.9, 136.0, 128.7, 128.6, 128.0, 127.7, 126.5, 123.2, 83.8, 70.7, 69.9, 53.4, 52.5. Anal. Calcd for $C_{21}H_{19}O_7$: C, 63.47; H, 4.82; N, 3.53. Found C, 63.72; H, 4.61; N, 3.62.

Ethyl 4-benzylidene-2-isopropyl-tetrahydrofuran-3,3-dicarboxylate (4p): oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.14 (M, 5H), 6.60 (s, 1H), 4.85 (dd, J = 13.8 and 2.2, 1H), 4.63 (dd, J = 13.8 and 2.6, 1H), 4.36−4.14 (M, 4H), 1.83 (m, 1H), 1.34 (d, J = 7.1, 3H), 1.25 (d, J = 7.1, 3H), 1.05 (t, J = 7.0, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.8, 168.4, 140.5, 136.4, 128.6, 128.5, 127.4, 124.1, 89.4, 70.0, 67.2, 61.8, 61.5, 30.5, 20.0, 19.9, 14.1. Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.30; H, 7.56. Found C, 68.98; H, 7.96.

Ethyl 4-benzylidene-2-phenyl-5-(2,3,4-trimethoxy)phenyl-tetrahydrofuran-3,3-dicarboxylate (4s): An oil containing a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55−6.75 (M, 24H), 6.56 (d, J = 8.8, 1H), 6.51 (s, 1H), 6.45 (d, J = 8.8, 1H), 6.31 (s, 1H), 5.96 (s, 1H), 5.83 (s, 3H), 4.40 (m, 4H), 3.98−3.68 (M, 20H), 3.49 (m, 2H), 1.40 (t, J = 7.0, 3H), 1.33 (t, J = 7.0, 3H), 0.83 (t, J = 7.0, 3H), 0.80 (t, J = 7.0, 3H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.9, 168.8, 168.7, 168.5, 154.2, 153.5, 152.9, 142.8, 141.7, 140.9, 139.3, 137.4, 137.2, 135.9, 135.5, 129.1, 128.9, 128.7, 128.3, 128.1, 128.0, 127.8, 127.5, 127.4, 127.1, 126.9, 125.3, 125.2, 123.6, 123.2, 107.7, 106.6, 83.8, 81.1, 77.3, 75.9, 70.9, 70.7, 62.0, 61.9, 61.6, 61.5, 61.3, 61.0, 60.9, 60.7, 56.2, 55.9, 14.2, 14.1, 13.5, 13.4. Anal. Calcd for $C_{32}H_{34}O_5$ (mixture of isomers): C, 70.31; H, 6.27. Found C, 69.83; H, 6.66.

Ethyl 4-(1-phenyl-ethylidene)-2-(4-nitro)phenyl-tetrahydrofuran-3,3-dicarboxylate (6) and ethyl 4-methyl-2-(4-nitro)phenyl-5-phenyl-3,6-dihydro-2*H*-pyran-3,3-dicarboxylate (7): isolated as an inseparable mixture, in a ratio of 4:1. Data for **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, J = 8.8, 2H), 7.68 (d, J = 8.8, 2H), 7.40−7.15 (M, 5H), 5.83 (s, 1H), 4.43 (s, 1H), 3.93 (s, 3H), 3.26 (s, 3H), 2.04 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 168.1, 147.7, 144.6, 142.9, 136.4, 132.5, 128.5, 127.8, 127.1, 122.9, 85.9, 72.0, 68.6, 53.3, 52.3, 22.0. Data for **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J = 8.8, 2H), 7.55 (d, J = 8.8, 2H), 7.40−7.15 (M, 5H), 5.49 (s, 1H), 4.53 (m, 2H), 3.83 (s, 3H), 3.56 (s, 3H), 1.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 147.4, 146.3, 137.3, 135.7, 128.6, 127.7, 125.8, 122.8, 79.4, 70.8, 64.3, 52.8, 17.4. HRMS *m*/*z* calcd for $C_{22}H_{21}NO_7$ (mixture of isomers) 411.1318, found 411.1319.

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Supporting Information Available: Complementary characterization for compounds **4** including copies of ^{1}H NMR spectra for **4b**−**f**, **4i**−**j**, **4l**−**n**, **4q** (two isomers), and **4r**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0012997

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